Communications to the Editor

Nuclear Magnetic Resonance $J(^{31}P-^{1}H)$ and (p → d)-π Interactions in Group IV Phenylphosphines

Sir:

We report $J(^{31}P-^{1}H)$ data for a series of group IV phenylphosphines analogous to the aniline-^{15}N derivatives which we studied by nmr to test the hypothesis of (p → d)-π contributions to the bonds between the elements of groups IV and V.[1] The one-bond $^{15}N-^{1}H$ coupling constants in substituted anilines increase with the substitution of groups which are capable of conjugation either on the phenyl ring[2] or at the nitrogen itself.[3] N substitution by silyl, germyl, and stannyl groups capable of d-orbital conjugation, however, results in the lowering of the $J(^{15}N-^{1}H)$ value below that in aniline itself, and two *N*-trimethylsilyl groups reduce the value still further.

As in the nitrogen case, substitution of conjugating groups on phosphorus increases $J(^{31}P-^{1}H)$. For example, while methyl substitution of PH_3 raises the magnitude of the coupling from 183[4] to 187.8[5] Hz (~2%), phenyl substitution gives rise to a larger increase (~13%) and substitution of phenylphosphine by a second phenyl group raises this value still further (to 214[6] Hz). Substitution of silicon, germanium, or tin for hydrogen in phenylphosphine should then raise the value of $J(^{31}P-^{1}H)$ if (p → d)-π conjugation is important.

The *tert*-butyl group was attached to phosphorus by the method of Crofts and Parker.[7]

$$(CH_3)_3CCl + C_6H_5PCl_2 + AlCl_3 \longrightarrow C_6H_5\underset{\displaystyle Cl}{\overset{\displaystyle Cl}{P}}C(CH_3)_3{}^{+}AlCl_4^{-} \xrightarrow{H_2O} C_6H_5\overset{\displaystyle O}{\overset{\displaystyle \|}{P}}C(CH_3)_3 \xrightarrow{LiAlH_4} C_6H_5\underset{\displaystyle H}{\overset{\displaystyle Cl}{P}}C(CH_3)_3 \quad (1)$$

The reaction of *tert*-butyl chloride with monolithiophenylphosphine yields mainly *tert*-butane, but with the lower group IV chlorides the organometallic phenylphosphine is obtained.

$$C_6H_5PH_2 + n\text{-}C_4H_9Li \xrightarrow{-C_4H_{10}} C_6H_5PHLi \xrightarrow{(CH_3)_3MCl} C_6H_5\underset{\displaystyle H}{\overset{\displaystyle |}{P}}M(CH_3)_3 \quad (2)$$

where M = Si, Ge,[8] or Sn. The tin derivative is particularly susceptible to air oxidation, and we have measured the nmr parameters for the product of carefully controlled oxidation. The $J(^{31}P-^{1}H)$ value of 197.4 ± 0.5 Hz specifies the process as[9]

$$\underset{\displaystyle H}{\overset{\displaystyle |}{C_6H_5PSn(CH_3)_3}} + {}^{1}/_{2}O_2 \longrightarrow \underset{\displaystyle H}{\overset{\displaystyle |}{C_6H_5POSn(CH_3)_3}} \quad (3)$$

I II

Further controlled oxidation led to slow precipitation of what is likely to be the pentavalent phosphonate. Oxidation of triphenylstannyldiphenylphosphine proceeds directly to the insoluble ≥Sn—O—P(=O)< product; no intermediate could be isolated. The trivalent ≥Sn–O–P< compound was prepared separately and shown to oxidize readily.[10] We have prepared trimethylstannyldiphenylphosphine[11] and find it much less sensitive to oxidation than the monophenyl derivative.

The observation of separate resonances for the methyl protons of I and II (separated by 11.8 Hz) in a mixture at ambient temperatures, as well as the couplings $J(^{31}P-Sn-C-^{1}H)$ (1.9 ± 0.2 Hz), $J(^{31}P-O-Sn-C-^{1}H)$ (2.0 ± 0.1 Hz), $J(^{31}P-^{119}Sn)$ (538 ± 3 Hz), and $J(^{31}P-O-^{119}Sn)$ (720 ± 30 Hz), rules out exchange phenomena involving breakage of the tin–phosphorus bond being rapid with respect to the nmr times (in excess of 2×1.9 sec^{-1} or 12 sec^{-1}, taking the smallest of the couplings seen). Spectra recorded at 125° show the coalescence of the methyl resonance and the disappearance of $J(^{31}P-Sn-C-^{1}H)$ and $J(^{31}P-O-Sn-C-^{1}H)$, signaling more rapid exchange presumably involving the breakage of Sn–P and Sn–O bonds. Separate $J(^{31}P-^{1}H)$ couplings are seen even at 150°, ruling out rapid exchange processes involving that bond. The spectral changes are reversible with temperature, and similar phenomena involving Sn–N bonds have been studied in the tin amines.[12]

Table I shows that the organometallic phenylphosphines exhibit lower $J(^{31}P-^{1}H)$ values than either *tert*-butylphenylphosphine or phenylphosphine itself. Substitution of a second group capable of d-orbital conjugation as in $[(CH_3)_3Si]_2PH$ reduces the value still further. As in the nitrogen case, the (p → d)-π bonding hypothesis is not necessary to explain these data which change in a way opposite to that expected from d conjugation with phosphorus. Our findings for both the amines and phosphines are adequately dealt with by considering redistribution of electrons in the σ framework of the molecules only.

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Table I. J(E–H), Hz

	E = ^{15}N[a]	E = ^{31}P[b]
$C_6H_5EH_2$	79–81	205.5[c]
$C_6H_5EHC(CH_3)_3$		205.7 ± 0.5
$C_6H_5EHSi(CH_3)_3$	76.0	200.6 ± 0.5
$C_6H_5EHGe(CH_3)_3$	77.1	194[d]
$C_6H_5EHSn(CH_3)_3$	73.8	187 ± 0.5
$[(CH_3)_2Si]_2EH$	66.5	186[e]

[a] Data taken from ref 1b. [b] Recorded on 20% solutions in benzene using a Varian HA-100D spectrometer. [c] Reference 9. [d] Reference 8. [e] E. Fluck, H. Burger, and V. Goetze, *Z. Naturforsch. B*, **22**, 912 (1967).

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β-Lactam Antibiotics from *Streptomyces*

Sir:

Several taxonomically unrelated true fungi produce penicillins,[1] and one species of *Streptomyces* has been reported to yield penicillin N.[2] Cephalosporin C (**1**) has been isolated from only one species of *Cephalosporium*.[3] We report here the identification of penicillin N, and isolation and structure elucidation of three new β-lactam antibiotics of the cephalosporin C type from two species of *Streptomyces*. Metabolite **2** was produced by a strain of *Streptomyces lipmanii* NRRL 3584. A new streptomycete species,[4] *Streptomyces clavuligerus* NRRL 3585, afforded antibiotics **3** and **4**.

The antibiotics present in the broth filtrate were concentrated by carbon and anion exchange resin column chromatography. Final purification was achieved by chromatography on cellulose and silica gel to yield the purified antibiotics. The three antibiotics exhibited some common properties. All had a band at about 1770 cm^{-1} in the ir spectra, suggesting the presence of a β-lactam carbonyl group.[5,6] The uv spectra showed absorption maxima at *ca.* 260 nm, characteristic of the 3-cephem chromophore[3,7,8] (Table I). Potentiometric titration revealed the presence of three ionizable groups, and amino acid determination on acid hydrolysates by the Spackman–Stein–Moore method[9] yielded about 2 μmol/mg of α-aminoadipic acid. An acetyl determination with **2** gave a value of 9.0%. Alkoxyl analysis of **2** and **4** afforded 4.5 and 5.8% methoxyl, respectively.

Characteristic features of the nmr spectrum of cephalosporin C (**1**) are the three pairs of AB doublets originating from the vicinally coupled β-lactam protons (J = 4.7 Hz), and the geminally coupled 2-methylene and 3′-methylene groups (J = 18 and 13 Hz),[10] respectively. In addition, the spectrum exhibits the three-proton acetyl singlet and the multiplet due to the seven α-aminoadipyl protons (Table I). The nmr spectrum of **3** shows all the spectral characteristics of **1**, except that the three-proton acetyl singlet is absent. This suggests that the difference between the antibiotic **3** and cephalosporin C is in the functionality on the 3′-methylene group. The nmr spectra of the antibiotics **1** and **2** reveal that in cephalosporin C the H-6 proton occurs as a doublet at τ 4.86, while in **2** there is a one-proton singlet at 4.84, Further, in **2** there is a three-proton singlet at τ 6.47. This indicates that the β-lactam ring has been modified in **2**. The nmr spectrum of **4** shows a one-proton singlet at τ 4.81 and a three-proton singlet at 6.47, and the acetyl singlet is not present. Consequently, in antibiotic **4**, both the functionality on the 3′-methylene group and the β-lactam ring substitution are different from that of cephalosporin C. The presence of a methoxyl group in **2** and **4** is established by alkoxyl analysis and by the three-proton singlets at τ 6.47.[13] Chemical shifts of the one-proton singlets at τ 4.84 and 4.81 in **2** and **4** correspond closely to the chemical shift of the H-6 doublet of cephalosporin C. These data suggest that in **2** and **4** there is a methoxyl group at C-7 of the β-lactam ring.

Reaction of **2**, **3**, and **4** with chloroacetyl chloride and *N*-carbethoxyphthalimide afforded the corresponding *N*-chloroacetyl (**2a**, **3a**, and **4a**) and *N*,*N*-phthaloyl (**2b**, **3b**, and **4b**) derivatives. Potentiometric titration of these *N*-acyl derivatives shows they all contain two ionizable groups. A comparison of the dissociation constants of **1**, **2**, **3**, and **4** and their *N*-acyl derivatives reveals that the antibiotics **2**, **3**, and **4** contain the amino and the two carboxyl groups present in cephalosporin C.

Reaction of the *N*-chloroacetyl (**2a**, **3a**, **4b**) and *N*,*N*-phthaloyl (**2b**, **3b**, **4b**) derivatives of **2**, **3**, and **4** with diazomethane gave the corresponding *N*-acyl dimethyl esters **2c**, **3c**, and **4c**, and **2d**, **3d**, and **4d**, respectively. The chemical shifts of the 3′-methylene protons in the nmr spectra of the antibiotics **1**, **2**, **3**, and **4** and their *N*-acyl dimethyl esters are similar (Table II). Consequently, the groups deshielding the 3′-methylene groups should be structurally similar. The *N*-chloroacetyl derivative of **1** reveals a three-proton acetyl singlet at τ 8.0, while the corresponding derivative of **3** has a two-proton exchangeable singlet at 3.41. Whereas the *N*-chloroacetylcephalosporin C dimethyl

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